REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments, remarks, and enclosures herewith.

I. Status Of The Claims And Formal Matters

Claims 1, 4-15, and 17-78 are currently pending in the present application. Claims 4-9, 13-14, 17-19, and 22-79 are cancelled herein. The claims have been amended in part as suggested by the Examiner on page five of the Office Action. Namely, claim 1 has been amended to eliminate the "consisting of" language and to provide clarity by indicating the cytokines which may be antagonized by the polypeptides of claim 1. Furthermore, as suggested by the Examiner, the subject matter of claim 1 has been separated into separate claims. Namely, new claims 80 and 87 comprise subject matter of former claim 1 and new claims 81-86 and 88-93 have been added to provide the full scope of protection to which Applicant is entitled. Claim 12 and 21 have been amended to recite "An isolated compound" rather than "A compound". Support for the amended claims can be found throughout the specification, for example at paragraph 36 of the specification as published (US 2004/0204352). The Examiner is thanked for making these suggestions.

The Examiner is further thanked for indicating that Applicant's claim for priority is granted to April 30, 2002 based on the certified foreign priority document, UK 0209884.6, which was submitted June 16, 2008.

The Examiner is also thanked for indicating that the rejection of claims 1, 10-15, 20 and 21 under 35 U.S.C. § 112, first paragraph, has been withdrawn.

No new matter is added.

It is submitted that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims and the remarks herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the amendments and remarks are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. The Double Patenting Rejection is Overcome

The rejection of claims 1, 15 and 78 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30, 31 and 39 of co-pending application 10/579,113 is maintained. This is a provisional double patenting rejection.

The issue of whether there is indeed double patenting is contingent upon whether the remarks herewith are indeed considered and entered; and, if so, whether the Examiner believes there is overlap with claims ultimately allowed in the application. If, upon agreement as to allowable subject matter, it is believed that there is still a double patenting issue, a Terminal Disclaimer as to U.S. Patent Application 10/579,113 will be filed for the purposes of expediting prosecution.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

III. The Rejection Under 35 U.S.C. § 101 is Overcome

Claims 12-14 are rejected under 35 U.S.C. § 101 because allegedly the claimed invention is directed to non-statutory subject matter. In particular it is asserted that the claims, as recited, read on compounds that exist in nature, and encompass naturally occurring macromolecules such as proteins, DNA and antibodies. The rejection is respectfully traversed.

The Examiner is thanked for suggesting that the claims may be amended to indicate that the compounds are "isolated". Claim 12 has been amended as suggested. Claims 13-14 are herein cancelled thereby obviating the rejection in part.

Accordingly, reconsideration and withdrawal of the rejection of claims 12-14 under 35 U.S.C. § 101 is respectfully requested.

IV. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Overcome

Claims 1, 10-15, 20, 21 and 78 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is respectfully traversed.

Claim 1 is allegedly confusing because it recites in part (i) "comprises or consists of" and further in that it recites three parts (i – iii) which the Examiner suggests should be separate claims. Claim 1 is further rejected because the sequences of SEQ ID NOS: 16, 26, and 20 all contain an extracellular domain yet the claim additionally recites, "wherein the polypeptide additionally comprises an extracellular domain as recited in SEQ ID NO: 22".

Although Applicants do not agree, in the interest of furthering prosecution, claim 1 has been amended to eliminate the recitation, "or consists of". In addition, to provide further clarity, recitation to polypeptides consisting of the amino acid sequences of SEQ ID NOS:16, 26, 20; or

22 have been eliminated from claim 1 and are now recited in new claim 80. The amendments to claim 1 make it clear that what is claimed is an isolated polypeptide, which comprises the amino acid sequence as recited in SEQ ID NO:16 or SEQ ID NO:26, wherein the polypeptide functions as an antagonist of cytokine expression and/or secretion of a cytokine selected from the group consisting of TNF-α, IL-4 and IL-2, IL-6, IL-5, and IL-10. Moreover, new claim 80 is directed to an isolated polypeptide, which consists of the amino acid sequence as recited in SEQ ID NO:16, SEQ ID NO:26, SEQ ID NO:20; or SEQ ID NO:22, wherein the polypeptide functions as an antagonist of cytokine expression and/or secretion of a cytokine selected from the group consisting of TNF-α, IL-4 and IL-2, IL-6, IL-5, and IL-10. Further, new claim 87 is directed to an isolated polypeptide according to claim 1 or claim 2 fused to a heterologous polypeptide. Accordingly, the amendments to claim 1 along with new claims 80 and 87 obviate the rejection.

Claims 13 and 14 are rejected as indefinite under 35 U.S.C. § 112, second paragraph, because allegedly claim 13 is vague and indefinite in reciting, "A compound that either increases or decreases the level of expression or activity of a polypeptide...without inducing any of the biological effects of the polypeptide". The Examiner asserts that it is unclear how one can increase the biological activity of a polypeptide without inducing biological effects of said peptide. Claims 13 and 14 have been cancelled, thereby obviating the rejection.

Claim 78 is rejected under 35 U.S.C. § 112, second paragraph because allegedly it is unclear as written in that it depends from only part of claim 1 ("according to claim 1(iii)) and also because it recites "a fusion protein comprising a fragment which comprises or consists of the amino acid sequence as recited in SEQ ID NO:20 or in SEQ ID NO: 22 fused to a heterologous polypeptide." Claim 78 has been herein cancelled, thereby obviating the rejection

In light of the amendments to the claims discussed above, the rejections under 35 U.S.C. § 112, first paragraph, are now moot. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph, are respectfully requested.

V. The Rejections Under 35 U.S.C. § 112, First Paragraph, Are Overcome

Claims 1, 10-15, 20, 21 and 78 stand rejected under 35 U.S.C. § 112, first paragraph, because allegedly claim 1 is not enabled. The Examiner asserts that in its present form, claim 1 can reasonably be interpreted as being drawn to a fusion protein comprising a fragment of any one of SEQ ID NOS: 16, 20, or 26 fused to a heterologous polypeptide which functions as an antagonist to expression and/or secretion of any cytokine. Allegedly, the specification does not

provide adequate guidance as to how to make and/or use functional fragments of the claimed polypeptides. The rejection is respectfully traversed.

Initially, claims 13, 14, and 78 have been cancelled, thereby obviating the rejection in part.

35 U.S.C. §112, first paragraph, requires that the specification describe how to make and use the invention. 35 U.S.C. §112, first paragraph, recites, in pertinent part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same[.]

A patent claim is invalid if it is not, *inter alia*, supported by an enabling disclosure. The test for enablement requires a determination of whether any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400, (Fed. Cir. 1988). The factors involved in determining whether there is sufficient evidence to support a finding of enablement include, among others, (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404.

Applying the law to the instant facts, all of the pending claims are enabled. Claim 1 has been amended to recite to an isolated polypeptide, which comprises the amino acid sequence as recited in SEQ ID NO:16 or SEQ ID NO:26, wherein the polypeptide functions as an antagonist of cytokine expression and/or secretion of a cytokine selected from the group consisting of TNF-α, IL-4 and IL-2, IL-6, IL-5, and IL-10. Support for these amendments may be found, for example, in Example 4 demonstrating *in vitro* inhibition of secretion of certain cytokines by ConA-stimulated human peripheral blood mononuclear cells. Thus the objected-to "fragment" and "any cytokine" language has been eliminated and/or replaced with recitations that render the claims fully enabled.

Moreover, and for the avoidance of doubt, Applicants submit herewith the Declaration of inventor Dr. Ursula Boschert ("the Declaration") demonstrating that the Applicant has conducted experiments to show that INSP052 can downregulate the secretion of cytokines such as TNF-α, IL-4 and IL-2, which indicates that INSP052 may be used to treat anti-inflammatory and autoimmune diseases. Furthermore, the Applicant has shown that INSP052 can be used to treat fulminant hepatitis by decreasing levels of TNF-α, IL-4 and IL-2 in a live mouse model (*see* Example 5). In addition, the Declaration relates to experiments carried out using the extracellular domain of INSP052, the INSP052EC protein, referred to in the present application as SEQ ID NO: 22, the cloning and expression of which is described in examples 2 and 3 of the pending application. This region is found in the INSP052 protein (SEQ ID NO: 16), and so the full length protein would share the activity identified for the active fragment upon which the experiments are based, as would other fragments containing the extracellular domain.

Example 1 from the Declaration demonstrates how INSP052 modulates cytokine expression in a live mouse model. Such mouse models involving LPS-induced cytokine release are frequently used as a model for fulminant hepatitis treatment. INSP052EC is shown to decrease expression of IL-6 and TNFa. This indicates that INSP052EC could be used to treat fulminant hepatitis.

In Example 2 of the Declaration, INSP052EC is shown to reduce ear swelling in a model of contact hypersensitivity. This demonstrates that INSP052 is useful in treating T cell-mediated inflammation of the skin, such as found in contact dermatitis and psoriasis.

Therefore, the experimental evidence provided in the Declaration shows that INSP052 is useful in treating various autoimmune/inflammatory disorders, confirming the description present in the specification regarding the usefulness of such polypetides in treating these disorders.

INSP052 is also identical to a protein described in the literature as Hepatocyte cell adhesion molecule (hepaCAM). Post-published documents such as Moh and Zhang *et al.* (attached) and Moh and Lee *et al.* (attached) provide further evidence of the role of INSP052 in wound healing. Moh and Zhang *et al.* discloses that hepaCAM increases cell spreading on the matrices fibronectin and matrigel as well as delaying cell detachment and enhancing wound healing in an in vitro wound healing assay, while Moh and Lee *et al.* shows that hepaCAM encodes an Ig-like transmembrane glycoprotein and is involved in cell adhesion and growth

control. Both of these references further confirms Applicant's description of the utility of the INSP052 protein.

Moreover, one of the inventors of the present application, in collaboration with other employees of the Applicant, has recently published a paper where INSP052 is referred to as GlialCAM (Favre-Kontula *et al.*, copy enclosed). This publication shows the expression of GlialCAM in glial cells of the central nervous system and their results suggest a multifunctional role for this protein in the formation and maintenance of the myelin sheath, as well as in astrocyte and CSF/CNS barrier function.

Thus, when the confirmatory data attached as the Declaration and the enclosed references are considered, in view of the fact that the techniques used in the present application allow highly accurate predictions of protein function to be made, the claims are clearly enabled.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph, are respectfully requested.

VI. The Rejections Under 35 U.S.C. § 102(e) Are Overcome

Claims 1, 10-15, 20, 21 and 78 remain rejected under 35 U.S.C. § 102(a) and (e) as being anticipated by Baughn, *et al.* (WO 02/40671). Allegedly, Baughn *et al.* discloses sequences identical to SEQ ID NOs: 16, 20, 22, and 26 or a portion thereof as well as fusion proteins comprising a fragment of SEQ ID NOs: 16, 26, or 20 wherein the polypeptide comprises an extracellular domain as recited in SEQ ID NO: 22. The rejection is respectfully traversed.

Initially, claims 13, 14, and 78 have been cancelled, thereby obviating the rejection in part.

It is respectfully submitted that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure of the claimed invention. *See Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990).

The Office Action asserts that Baughn *et al.* teaches a polypeptide, identified as IGSFP-4, which is 100% identical to amino acids 1-240 of SEQ ID NO: 20 and comprises a polypeptide (amino acid residues 34-240) which is 100% identical to SEQ ID NO: 22. Additionally, Baughn *et al.* allegedly teaches a polypeptide (AAD14784) comprising a sequence which is 100% identical to amino acids 1-291 of SEQ ID NO: 16. Further, this sequence is allegedly 100%

identical to amino acids 1-258 of SEQ ID NO: 26. Thus, the Office Action asserts that Baughn *et al.* teaches a polypeptide which comprises fragments of SEQ ID NOs: 16, 26, or 20 and comprises the amino acid sequence of SEQ ID NO: 22.

Claim 1 now recites to an isolated polypeptide, which comprises the amino acid sequence as recited in SEQ ID NO:16 or SEQ ID NO:26, wherein the polypeptide functions as an antagonist of cytokine expression and/or secretion of a cytokine selected from the group consisting of TNF-α, IL-4 and IL-2, IL-6, IL-5, and IL-10. Moreover, new claim 80 is directed to an isolated polypeptide, which consists of the amino acid sequence as recited in SEQ ID NO:16, SEQ ID NO:26, SEQ ID NO:20; or SEQ ID NO:22, wherein the polypeptide functions as an antagonist of cytokine expression and/or secretion of a cytokine selected from the group consisting of TNF-α, IL-4 and IL-2, IL-6, IL-5, and IL-10. New claim 87 is directed to an isolated polypeptide according to claim 1 or claim 2 fused to a heterologous polypeptide.

As indicated in the Office Action, Baughn *et al.* fails to provide full length sequences for SEQ ID NOS: 16, 20, and 26. Instead, Baughn *et al.* only discloses amino acids 1-291 of SEQ ID NO: 16 and amino acids 1-258 of SEQ ID NO: 26. Indeed, Baughn *et al.* does not disclose the full length INSP052 sequence, since it would not have been possible to identify full length INSP052 using conventional techniques. If it were possible to identify INSP052 using conventional techniques, the skilled person would have expected the authors of Baughn *et al.* to have identified the full length protein, rather than merely a fragment of it.

Furthermore, Applicants submit that analysis of an alignment between SEQ ID NO: 20 and SEQ ID NO: 22 of the present application, and the sequence of AAD14784 from Baughn *et al.* (Exhibit 1) shows that over its 298 amino acids length, while the sequence of Baughn *et al.* may comprise amino acids 1-240 of SEQ ID NO: 20 and amino acids 1-207 of SEQ ID NO: 22, it fails to disclose polypetides consisting of either sequence, as required by new claim 80 (subject matter of which was formerly in claim 1). Thus, Baughn *et al.* does not contain all of the elements of the claims as presented herein and therefore cannot anticipate the present claims.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 are respectfully requested.

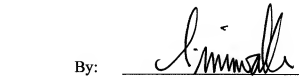
REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, prior to issuance of any paper other than a Notice of Allowance, an interview, is respectfully requested, with the Examiner and the Examiner's supervisor, and, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the amendments, remarks and enclosures herein, the application is in condition for allowance. Reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance, is respectfully requested.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

Thomas J. Kowalski
Reg. No. 32,147
Ljiljana Minwalla, Ph.D.
Reg. No. 60,569
(212) 588-0800